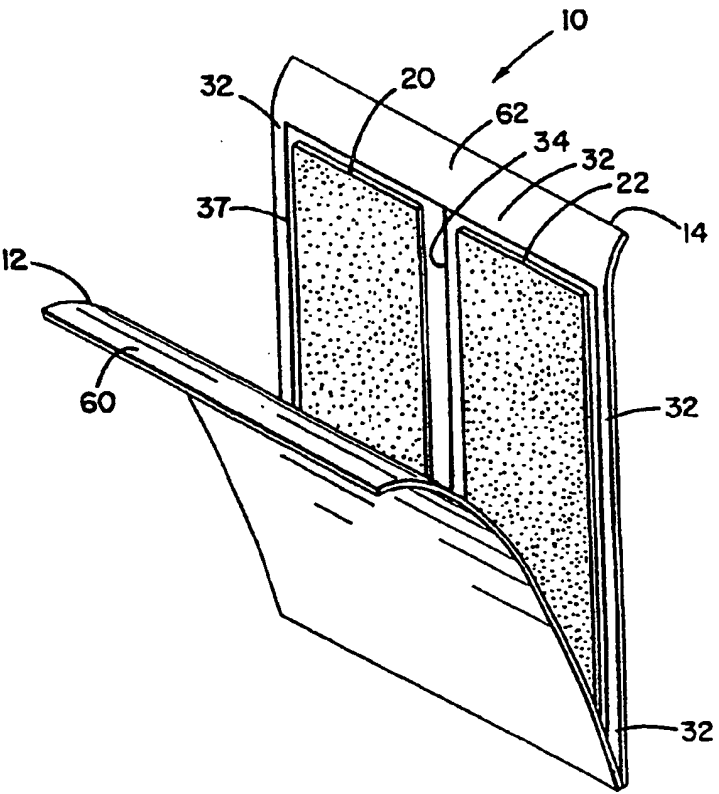




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61M 35/00	A1	(11) International Publication Number: WO 94/13354 (43) International Publication Date: 23 June 1994 (23.06.94)
<p>(21) International Application Number: PCT/US93/11897</p> <p>(22) International Filing Date: 7 December 1993 (07.12.93)</p> <p>(30) Priority Data: 07/986,597 7 December 1992 (07.12.92) US 08/117,444 7 September 1993 (07.09.93) US</p> <p>(71) Applicant: CREATIVE PRODUCTS RESOURCE, INC. [US/US]; 132 West Greenbrook Road, North Caldwell, NJ 07006 (US).</p> <p>(72) Inventors: SMITH, James, A.; 85 Watch Hill Way, Chatham, MA 02633 (US). MURPHY, Betty, J.; 64 Dryden Road, Upper Montclair, NJ 07043 (US).</p> <p>(74) Agent: BRUESS, Steven, C.; Merchant, Gould, Smith, Edell, Welter & Schmidt, 3100 Norwest Center, 90 South Seventh Street, Minneapolis, MN 55402 (US).</p>		<p>(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: IN-TANDEM APPLICATOR PADS FOR THERAPEUTIC AGENTS</p>		
<p>(57) Abstract</p> <p>The invention provides a method for applying a plurality of compositions, preferably two, containing a dermatological or other therapeutic agent to the skin from a single dispensing and applicator system (10). The system (10) has a plurality of compartmentalized applicator pads (20) and (22) which may be exposed and sequentially or simultaneously applied to the skin area to be treated. The system (10) is useful for administering separate phases of an occlusive or semi-occlusive film forming solution for treating pathologies of the skin. When the phases are applied to and dried upon the skin, a polymeric film forms to retain the therapeutic agent in contact with the surface of the skin.</p> 		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

IN-TANDEM APPLICATOR PADS FOR THERAPEUTIC AGENTS

FIELD OF THE INVENTION

5 The invention is directed to a method for containing, protecting, dispensing and applying substances such as solid and flowing substances, and more particularly, to a method for dispensing and applying two or more dermatological agents either simultaneously or sequentially.

10 The invention also provides a method for applying a plurality of separate phases of a composition containing a therapeutic agent, for example, an occlusive or semi-occlusive film-forming solution for treating pathologies of the skin.

15

BACKGROUND OF THE INVENTION

A wide variety of packages are used to contain and protect a substance until it is desired to release and dispense the substance from the package. Several methods

20 exist for dispensing and applying various solid substances or articles, such as powders, pills, granules and other shaped substances. Said methods may also be used to dispense and apply various flowable substances such as gels, solutions, dispersions, and other dimensionally unstable

25 substances. In some cases, it may be desirable to include structure as part of the package which assists in dispersing or applying the contents. Oftentimes, the package includes an applicator for directed application of the contents, as they are dispensed from the package.

30 Several factors are taken into consideration in providing a method for dispensing a flowable or solid substance. One concern is the performance characteristics of the dispensing package. For example, the ease with which the package can be opened and its contents expelled can be

35 important. The ability of the package to store and contain a substance prior to its application is another factor.

When an applicator such as an absorbent pad or sheet is included as part of the package, secure attachment of the applicator to the packaging can be important so that the applicator does not become disengaged during use.

5 Various packages have been developed to contain and dispense solutions, dispersions or gels of various active ingredients. One such dispenser is an envelope-like package that defines an internal reservoir for containing a fluid. For example, U.S. Patent No. 4,427,115 to Laipply,
10 discloses a packaging device for applying various fluids to the skin. The device is made of a flexible sheet of fluid impermeable material that is folded in half and sealed around the edges in a temporary seal. The two halves of the sheet are pulled apart to break the seal and form a flat
15 surface covered with the fluid. An absorbent pad may be adhered inside the chamber to aid in the retention and delivery of the fluid.

Other packaging systems provide for a cup-like reservoir with a foil or paper covering that is torn off to
20 expose the fluid or other material contained within the chamber. For example, Canadian Patent No. 613,023 to Wilson et al. disclose a creamer-type dispenser with a wide-mouthed cup and a covering sheet sealed over the mouth of the cup. The covering sheet has a tab adhesively sealed over a flat
25 extension of the rim of the cup. The package is opened by pulling the tab of the covering sheet upward off the rim extension and inward toward the cup. U.S. Patent
No. 3,860,348 to Doyle et al. disclose a cup with a foil covering over the mouth and a liquid-impregnated sponge
30 attached to the inside of the cup. When the covering is peeled off the rim of the cup, the sponge projects outward through the opening.

U.S. Patent No. 4,372,098 to Mason discloses an applicator package with a pair of side panels, one of which has a recessed portion for receiving an absorbent pad which is secured to the side panel within the central recessed portion. The applicator means sealed within the package by sealing the edged portion of the side panel in surrounding relation to the applicator means thereby enclosing and hermetically sealing the applicator means within the side panels. One of the edged portions of the side panels is then secured to enable the side panels to be gripped at that area and separated from each other so as to expose the applicator means.

U.S. Patent No. 4,796,751 to Madkour discloses a portable eyeglass cleaning kit which comprises a generally flat flexible container having two separate compartments which are separably operable to make available the lens cleaning medium and the lens wiping medium. The cleaning and wiping media are sheets of absorbent material such as woven or unwoven fabric or tough liquid absorbent paper. The cleaning and wiping media are not affixed to the container and are separably removable from the compartments of the container. The container is made of a moisture and gas impervious sheet material such as metal foil, treated paper or plastic film. The container is operable by tearing along a scored line or by separation of the sealed edges.

Packages have also been developed to expel the contents of an inner chamber through a fracture or score line in one surface of the package. The ends of the package are forced together to expand and rupture the score line. For example, U.S. Patent No. 3,968,630 to Reimond discloses a dispensing package having a single reservoir with a pattern of perforations cut partially through the surface on one side of the package that is covered with a foil sealant.

A further consideration in designing a useful dispensing system is the ability to deliver more than one substance from a unitary system. Also desirable is a packaging system that is useful to simultaneously combine and dispense a plurality of substances, each requiring separate storage until being combined, due to their physical or chemical incompatibility.

To accomplish this, several applicator systems with a prescored fracture line in one surface of a package provide for reservoirs in discrete portions of a single package. For example, U.S. Patent No. 4,140,409 to DeVries discloses a package system for containing and dispensing liquids and other flowable materials comprising a reservoir chamber in each half of an elongated package. A prescored fracture line in one surface of the package ruptures when the ends of the package are urged together, and the contents of the chambers are expelled into an applicator sponge that is attached to the outside of the package. However, a disadvantage of packages with such externally placed applicators is that the applicator may become soiled or detached. Also, where a sterile applicator is desired, such a package system may not maintain the applicator under sanitary conditions prior to use.

A covering may be provided to enclose an externally attached applicator. For example, U.S. Patent No. 4,430,013 to Kaufman discloses a package system that has an interior chamber for containing a fluid, a score line in one surface of the package, and an applicator mounted over the score line. An overwrap with a fracture line on one surface encloses the package and the applicator. When the package is folded in half, the score line is broken and the fluid in the reservoir chamber is expelled into the applicator. The applicator then bursts through the fracture line in the overwrap.

In accordance with this packaging system, the liquid substance is contained and stored within a reservoir separately from the applicator until the package is opened. A drawback of this system is that to dispense the substance from the package, the reservoir chamber must first be opened, and the substance must be ejected therefrom and then dispersed into and through the applicator, which can result in uneven wetting of the applicator. In addition, problems may occur because of premature leakage or evaporation of the liquid contents from the inner chamber of the dispensing package into the external applicator due to a premature break in the fracture line. If the overwrap becomes torn or punctured, the applicator may become uncovered and contaminated, and the liquid substance prematurely dispensed.

To provide a more secure containment, the applicator may be enclosed within a more rigid package. Kaufman also discloses a package system in which an applicator is attached to the inside of a package that has a score line on one surface. The applicator is compressible and sponge-like with a protruding thickened portion placed against the score line. A rib projection is provided on the inside surface of the package opposite the score line to help push the applicator out through the score line when the package is folded. A drawback is that the package cannot be reclosed or resealed with the applicator contained inside once the fracture line is separated and the applicator extruded.

U.S. Patent No 4,812,067 to Brown et al. also provide a system that provides separate reservoir chambers in a flexible package. The chambers are compressed to rupture an internal seal in the package which urges the liquid contents into a central dispensing cavity. The ends of the package are bent backward to split open a score line in the surface of the package. Pressure on the package

forces the contents to be expelled through the slit in the score line and onto a sponge attached to the outside of the package.

A disadvantage of packaging devices that release their contents by rupturing a score line in the container wall is that flexing of the package prior to use may cause the fracture line to split apart prematurely, thus causing unwanted leakage or premature dispersal of the contents. Conversely, the score line may be constructed such that it is difficult to break.

Therefore, there is a need for a method of dispensing system which addresses the above-mentioned problems of prior dispensing systems. In particular, there is a need for a packaging system for dispensing flowable and/or solid substances which has an improved configuration for releasing the contents of the packaging that is not prone to premature rupture, but provides ready dispensing of the package contents. There is also a need for a packaging that is a convenient means of dispensing a plurality of flowable and/or solid substances from multiple chambers within the packaging system, to overcome the physical or chemical incompatibility of the substances, to allow for separation of ingredients until the desired application, or to allow for sequential application of substances.

25

SUMMARY OF THE INVENTION

The present invention provides a novel method for containing, dispensing and applying to a target surface, two or more substances such as solids, powders or granules, and/or flowable substances such as gels, suspensions, dispersions or solutions.

In one embodiment of the invention, there is provided a method for applying a plurality of dermatological agents to the skin from one dispensing and applicator system comprising the steps of (1) providing a dispensing and

applicator system comprising a flexible, moisture impermeable support sheet; a plurality of applicator pads affixed in a separated array to one surface of the support sheet, each of the pads being impregnated with a composition comprising a different dermatological agent in combination with a compatible carrier; and a flexible, moisture impermeable cover sheet having its peripheral surface releasably sealed to the opposed peripheral surface of the support sheet so as to form a compartment containing the pads and defined by a continuous seal, which seal is positioned inwardly from the edges of the sheets over a portion of the opposed peripheral surfaces, so as to form two opposed flanges; (2) manually grasping and separating the flanges to at least partially release the cover sheet from the support sheet, so that the pads are exposed; and (3) contacting one or more of the pads with the skin to release the compositions sequentially or essentially simultaneously from the pads, to thereby apply a film of a mixture of the dermatological agents onto the skin.

20 In another embodiment of the invention, the cover sheet and the support sheet are releasably sealed together between the pads to divide the compartment into a plurality of subcompartments, each containing a single pad. In still another embodiment, the cover sheet or support sheet is scored along lines between the pads so that, in step (2), the flanges abutting one subcompartment are separated so that the cover sheet or support sheet tears along the score lines and separates from the other sheet to open one subcompartment and expose one of the pads, while the other subcompartments remain intact; and so that in step (3), the exposed pad is contacted with skin to release the composition from the exposed pad onto the skin.

For example, the present applicator system is particularly well-adapted to contain, preserve and to sequentially or simultaneously deliver two or more chemically or physically incompatible active ingredients. Preferably, the two-pad applicator will be used to contain, preserve and deliver unit doses of two cosmetic or pharmaceutical ingredients intended for topical application to the skin, e.g., dermatological agents, such as are used to treat a disorder such as acne, dermatitis, including atopic dermatitis, insect bites, diaper rash, sunburn, burns, eczema, psoriasis, poison ivy rash, poison oak rash, poison sumac rash, rashes or other skin irritation due to cosmetics, detergents or jewelry and the like.

In yet another embodiment of the invention, a single dispensing and applicator system is used for applying at least two phases of a film-forming composition comprising a therapeutic agent to the skin. The method includes the steps of (a) providing a dispensing and applicator system comprising a support sheet, a plurality of applicator pads affixed to the support sheet, and an impermeable cover sheet sealed to support sheet to form a compartment containing the pads, as described hereinabove, wherein each of the pads are impregnated with a different phase of the film-forming composition, a first phase made of a solution of a barrier polymer, and a second phase made of one or more emollient oils; (b) releasing the cover sheet from the support sheet to exposed the pads, as described hereinabove, and (c) contacting two or more of the pads with the skin to release the phases of the film-forming composition, sequentially or essentially simultaneously from the pads, at least one pad being impregnated with the first phase (polymer solution), and at least one pad being impregnated with the second phase (emollient solution), at least one of the solutions containing an effective amount of the therapeutic agent, such that a mixture of the solutions is

applied to the skin to form an occlusive or semi-occlusive film over the skin, with the film retaining the therapeutic agent in intimate contact with the skin for transdermal delivery.

5 Novel dispensing and applicator systems are also within the scope of the invention.

These and other advantages of the invention over conventional dispensing and application methods will become more apparent after reading the description and claims which
10 follow.

All percentages are weight percentages (wt-%) unless otherwise indicated. As used herein, the term "dermatological agent" includes bioactive compounds such as antibiotics and peroxides, as well as compounds intended
15 primarily for cosmetic purposes, such as emollients and sunscreens.

BRIEF DESCRIPTION OF THE DRAWINGS

Throughout the following views, reference numerals
20 will be used on the drawings, and the same reference numerals will be used throughout the several views and in the description to indicate same or like parts of the invention.

Figure 1 is a perspective view of a first
25 embodiment of the dispensing device of the invention shown in the closed position.

Figure 2 is a perspective view of a first embodiment of the dispensing device of the invention shown in the partially open position.

30 Figure 3 is a perspective view of a second embodiment of the dispensing device of the invention shown in the closed position.

Figure 4 is a perspective view of a second embodiment of the dispensing device of the invention shown
35 in the partially open position.

Figure 5 is a perspective view of a third embodiment of the dispensing device of the invention shown in a partially open position.

5 DETAILED DESCRIPTION OF THE INVENTION

Referring now to Figures 1 and 2, one embodiment of the dispensing and applicator device, designated generally by the numeral 10, is shown according to the present invention. As depicted, dispensing and applicator
10 device 10 is of a generally rectangular configuration. It will be understood, however, that a variety of shapes and sizes can be accommodated according to the invention. Referring to Figures 1 and 2, dispensing and applicator device 10 is shown having a cover sheet 12 and a support or
15 backing sheet 14. The cover sheet 12 and support sheet 14 each have peripheral edges 30, 32 extending completely around the cover sheet 12 and support sheet 14, respectively. Integral with peripheral edges 30, 32 are flanges 60, 62 for gripping in order to separate cover sheet
20 12 from support sheet 14 to open the dispensing and applicator device 10.

Applicator pads 20, 22 are arranged in a separated array, such as being positioned adjacent to each other in a side-to-side arrangement on support sheet 14. Optionally,
25 recessed areas (not shown) may be provided in support sheet 14 to receive applicator pads 20, 22. Applicator pads 20, 22 are attached to the surface of support sheet 14 by known techniques in the art. Applicator pads 20, 22 may be made, as for example, of a plastic foam, sponge, woven or nonwoven
30 natural or synthetic fiber or fabric, including gauze, felt or cotton or other material capable of absorbing a liquid or flowable composition. Another applicator useful according to the invention is, for example, a sheet of plastic or stiff paper having pores through which a powder or granular
35 substance, or flowable substance, may be dispensed.

In order to enclose the applicator pads 20, 22 within the dispensing and applicator device 10, opposed peripheral edges 30, 32 of cover sheet 12 and support sheet 14 are releasably sealed together in surrounding relation to applicator pads 20, 22, along continuous peripheral seal line 37, thereby defining a compartment within which the applicator pads 20, 22 are enclosed and sealed. Preferably, a center seal 34 may be provided between pads 20, 22 in order to divide the compartment into two subcompartments, each of which encloses and isolates one applicator pad from the other. Any suitable means of sealing, such as those discussed below, may be utilized.

The flanges 60, 62 of cover sheet 12 and support sheet 14 are created by positioning the peripheral seal line 37 inward from at least a pair of abutting edges of cover sheet 12 and support sheet 14. Flanges 60, 62 provide a means for gripping cover sheet 12 and support sheet 14 to facilitate the opening of dispensing and applicator device 10 by pulling cover sheet 12 apart from support sheet 14 and thus exposing applicator pads 20, 22. While these flanges 60, 62 are shown as extending the entire length of one edge of device 10, it is readily apparent that flanges 60, 62 could be provided over a more limited area, such as only at one corner of cover sheet 12 and support sheet 14.

Figures 1 and 2 illustrate an integral one-piece cover sheet 12, positioned over support sheet 14 and applicator pads 20, 22. Referring to Figures 3 and 4, a second embodiment of the invention is shown wherein a score line 18 is provided on cover sheet 12 between applicator pads 20, 22 for detaching a portion of the cover sheet 12 along the score line from support sheet 14, in order to sequentially expose the pads. The score line 18 coincides with the center seal 34, which, in concert with peripheral seal line 37, divides the compartment into individual subcompartments for each pad 20, 22, and is provided to

allow a portion of cover sheet 12, 12", to be easily separated from the remainder of cover sheet 12, 12', and from support sheet 14. It is understood that score line 18 may be a fracture line, perforations or other like means to allow easy separation of the portion of cover sheet 12, 12' along the score line 18. Alternatively, as shown in Figure 5, the score line 18 may be provided on support sheet 14 to obtain sequential release of the pads 20, 22 each attached to portions 14', 14" of support sheet 14, while cover sheet 12 remains intact.

The material used for cover sheet 12 and support sheet 14 should be relatively puncture resistant, non-absorbent, and impermeable, chemically compatible and non-reactive with the flowable substance or material contained in the dispensing and applicator device 10 to prevent leakage or migration of the contents out of the dispensing and applicator device 10, and substantially impermeable to external contaminants such as air, dust, liquids and the like.

Suitable materials for cover sheet 12 and support sheet 14 should be materials capable of allowing cover sheet 12 to be sealed to support sheet 14 along peripheral edges 30, 32 in order to form a containing and dispensing package that does not separate during normal use. For example, cover sheet 12 and support sheet 14 may be made of a thermoplastic and heat sealable polymeric film material, such as polyethylene, polyvinyl chloride, or polyamide-type resins, according to known techniques in the art. Such a film may be used alone or adhered to a non-heat sealable material by known techniques. Cover sheet 12 and support sheet 14 may be formed, for example, of glassine paper, cellophane, polyethylene, polypropylene, polyvinyl chloride, polyester, nylon and the like. Cover sheet 12 and support sheet 14 may also be formed of an aluminum foil that is coated or sealed with a thermoplastic material such as a

polyethylene, polyester, polyvinyl resin or cellulose acetate. Alternatively, the foil may comprise a cellulosic material lined with a thermoplastic film or other synthetic or plastic material. A foil-lined paper board may also be
5 used. For examples of flexible materials suitable for cover sheet 12 and support sheet 14, see for example, "Coatings and Laminations," in Handbook of Package Engineering (2d ed.), pages 4-1 to 4-20, J. F. Hanlon, the disclosure of which is incorporated by reference herein.

10 Cover sheet 12 and support sheet 14 may also be formed of a laminate or covered with a lamination that includes components such as fluorohalocarbon (Aclar), cellulose acetate, cellophane, polyester, polyvinyl chloride (PVC), polyethylene (PE), polypropylene, rubber
15 hydrochloride, PVDC, and the like. A laminated cover sheet 12 and support sheet 14 may include, for example, paper or foil with polyester, acetate with foil and lacquer, acetate with metallized Mylar and polyester, and other suitable combinations that will provide, for example, a stiff yet
20 flexible cover sheet 12 and support sheet 14, a moisture or gas barrier, protection of the contents from photochemical change from exposure to light, prevention of plasticizers and stabilizers from the film by the contents of the package, and other like factors. For example, cover sheet
25 12 and support sheet 14 may be formed of a laminated paper board material such as a stiff cardboard that is covered with a foil material and/or a structured film. The layers of the lamination may be sealed together, as for example, by heat.

30 A coating to provide a nonporous gas and/or vapor barrier, as for example polyethylene and/or polyester, may be applied to the outer surface of cover sheet 12 and support sheet 14. The coating may provide a sealant to prevent entry of vapors or water, or evaporation of the
35 contents from dispensing and applicator device 10, such as

an organic solvent vehicle. Cover sheet 12 and support sheet 14 may be coated, for example, with a wax coating such as a paraffin wax alone or as part of a blend, as for example, with microcrystalline wax and polyethylene; a 5 varnish coating; a polyvinylidene chloride (PVDC) coating; a polyester (PET) coating, as for example, polyethylene terephthalate; a heat seal coating, as for example, with polyethylene, vinyl, acetate, polyvinyl resin or cellulose acetate, or other cellulosics, or polyvinyl chloride; an 10 extrusion coating, as for example, with polyethylene; or a metallized film coating, as for example, a metallized polyester, nylon, polyethylene, or polypropylene having a thin layer of aluminum. A coextruded or composite film may also be used to cover sheet 12 and support sheet 14. A 15 composite film may include, for example, polyethylene and polypropylene with nylon, EVA, saran, and/or styrene.

As stated above, support sheet 14 may be made of the same or similar material as that used for cover sheet 12, but preferably support sheet 14 is somewhat more rigid 20 than cover sheet 12. For example, support sheet 14 may additionally be made of synthetic organic polymeric sheet material such as polystyrene, acrylonitrile or acrylic copolymer with polystyrene, for example by extrusion, thermoforming, vacuum-forming, or other technique known in 25 the art. A coating to provide a nonporous gas and/or vapor barrier, as for example, a coating, a co-extruded plastic such as polyethylene and polyethylene terephthalate, or a laminate of these materials and others such as polypropylene, polyvinylidene chloride, cellophane, and the 30 like, may be applied to the outer surface of support sheet 14 as a sealant to prevent entry of vapors or water, or evaporation of the contents of dispensing and applicator device 10, such as an organic solvent.

Cover sheet 12 may be sealed to support sheet 14 to form seal lines 34, 37, by a heat seal, pressure seal, high frequency seal, ultrasonic seal, a crimp, a bonding material or various adhesive materials. Other suitable
5 attachment methods or means may be used to effect a secure seal according to known techniques in the art. For example, heat may be applied according to known techniques in the art to cause a bonding of the thermoplastic liner of support
10 sheet 14 to cover sheet 12. A temporary heat seal may be formed by applying relatively narrow lines of heat seal, and wider lines of heat seal may be applied to effect a more permanent seal. A permanent seal may also be provided by applying a high degree of heat using an appropriately high
15 temperature, and a lower degree of heat using a lower temperature to provide a temporary seal.

Adhesives used to form seal lines 34, 37 should be non-reactive and compatible with the materials used for cover sheet 12 and support sheet 14 as well as with the contents within the compartment or subcompartments of
20 dispensing and applicator device 10, and should not permit premature leakage or diffusion of such materials from the package. An example of adhesives for effecting a releasable seal include, for example, polyvinyl chloride (PVC) applied to one surface, and polyvinyl acetate applied to a second
25 surface. Cover sheet 12 and support sheet 14 may also be sealed together by a piece of material (not shown) attached between cover sheets 12 and support sheet 14.

It is understood according to the invention that applicator pads 20, 22 may each contain the same or
30 different substances. Advantageously, the dispensing and applicator device 10 of the invention may be used to dispense two or more substances that should be, or are preferably, kept separated until the desired application. The two components would then be dispensed according to the
35 invention simultaneously by the two applicator pads 20, 22

in the embodiment shown in Figures 1 and 2, or sequentially from one of the applicator pads 20, 22 at a time in the embodiment shown in Figures 3 and 4. A wide variety of different cosmetic or bioactive agents may be impregnated in 5 applicator pads 20, 22.

Use of the Dispensing and Applicator System.

Acne is a common inflammatory disease of human skin, and concentrates in skin areas where sebaceous glands 10 are largest, most numerous, and most active. In its milder types, it is a more or less superficial disorder which is evidenced by slight, spotty irritations and ordinary skin hygiene is a satisfactory treatment. However, in the more inflammatory types of acne, bacterial invasion of or about 15 the pilosebaceous follicles occurs and pustules, infected cysts and, in extreme cases, canalizing inflamed and infected sacs appear. These lesions may become extensive and leave permanent, disfiguring scars.

To reduce the severity of acne, various forms of 20 medication have previously been topically applied to the skin. Antibacterial soaps have been used as well as bactericidal agents such as sulfur and resorcinol. Other topical compositions have separately contained benzoyl peroxide, hexachlorophene, erythromycin or neomycin sulfate. 25 None of these prior preparations has been completely effective.

As disclosed by Klein et al. (U.S. Patent No. 4,497,794), it was discovered that a mixture on the skin of a peroxide, especially benzoyl peroxide and an antibiotic 30 or antibacterial such as clindamycin, neomycin, sodium sulfacetamide, sulfur, tetracycline or erythromycin is particularly beneficial as they can exert a statistically significant synergistic effect. Peroxides inhibit the formation of free fatty acids in the skin, primarily through 35 inactivation of extracellular lipase (via oxidation)

necessary to cleave triglycerides into free fatty acids and glycerol. The antibiotic or antibacterial component reduces the concentration of *Corynebacterium acnes* (i.e., *P. acnes*), a normal anaerobic bacteria which is the prime source of the lipase. Instead of the benzoyl peroxide, which is preferred, peroxides such as stabilized hydrogen peroxide and peroxides of organic acids, such as a lauroyl peroxide, may be used.

As disclosed by Klein et al., erythromycin and benzoyl peroxide may be applied to the skin in combination in a preformulated aqueous-alcoholic gel. However, if a mixture is first made up and then applied to the skin, it is best that the mixture be made at the time of application or that the mixture be used within twenty-four hours. The prompt use of a premix is necessary due to the chemical incompatibility of the two active agents. Because of this, it is advisable that the two agents be put in separate vials, bottles or other containers. For example, the Klein et al. patent discloses a kit containing, separately bottled liquid compositions comprising 5% benzoyl peroxide and a solution of erythromycin in ethanol or acetone.

However, separately packaging multiple dosages of the two active ingredients presents a number of disadvantages to the end-user. For example, a unit application dosage of each active must be removed sequentially from each container and absorbed onto an applicator, such as a cotton swab, so that it can be coated onto the skin of the user. This provides opportunities for spillage or over- or underdosing, which can lead to skin irritation and other side effects. Furthermore, such a multidose system necessarily adds to the costs of packaging, shipping and storage.

As can readily be ascertained from the foregoing description, the dispensing and applicator system is intended to overcome these difficulties. As exemplified, the present dual-pad package can readily contain, preserve
5 and deliver single unit doses of two or more chemically- or physically-incompatible active ingredients. For example, an antibiotic in combination with a liquid, semi-liquid (cream) or gelled aqueous or non-aqueous vehicle can be absorbed by and retained by the first pad and a second ingredient which
10 is physically- or chemically-incompatible with the antibiotic, such as a peroxide, can be absorbed and retained by the second pad, preferably in combination with the appropriate vehicle.

Alternatively, the present application system can
15 be used to contain and release two active ingredients which are desirably applied sequentially, whether or not they are physically or chemically compatible on the skin. Other examples of pairs of such ingredients include (a) an antibiotic or a peroxide for treatment of a skin disorder
20 and a keratolytic/antiseptic agent such as salicylic acid; (b) retinoic acid (Retin[®] A) and moisturizing agent to counteract the drying/scaling effects of the Retin[®] A, and/or a sunscreen to protect the skin against the increased sensitivity to the sun caused by the Retin[®] A;
25 (c) a pigmented, wax-based make-up composition, such as eyeshadow, blush, foundation bases and the like, or a sunscreen in a similar water-insoluble vehicle; and liquid make-up remover formulations that are formulated to remove the make-up or the sunscreen; (d) a steroid, preferably a
30 corticosteroid and a complementary dermatological agent, such as an antihistamine, antifungal, antibiotic and/or sunscreen; and (e) two phases of a film-forming solution for treating a skin disorder or disease, a first solution containing a barrier polymer and a therapeutic agent, and a
35 second solution containing emollients.

As can be readily seen from the figures, the present applicator is adapted to either simultaneously release and produce a mixture of two (or more) active ingredients on the target skin area to be treated, or to sequentially deliver unit doses of two or more active ingredients. This is accomplished by sequentially removing the covering sheets to expose the applicator pads, as it is desired to apply the active therefrom, while leaving the remaining pad or pads enclosed.

10 Although each pad will contain at least one active ingredient, preferably in combination with a suitable carrier vehicle, compositions containing multiple active, chemically compatible ingredients can be absorbed onto each of one or more of the pads.

15 The applicator is also adapted to deliver separate phases of a solution by simultaneous release onto the target skin area, or by sequential delivery of the phases to the skin. In such an application, the therapeutic agent may be incorporated into one or both phases, and absorbed into one
20 or more of the pads.

Peroxide Compositions for Acne Treatment

One pad in the present acne-treatment applicator system will preferably comprise an effective fatty acid-inhibiting amount of a peroxide, i.e., hydrogen peroxide or
25 an organic peroxide, preferably in combination with a gelled or semi-liquid (lotion or cream) vehicle.

No matter what vehicle is employed, on a weight basis, the selected antibiotic (clindamycin, tetracycline
30 and/or erythromycin) and the selected peroxide should be measured out so that as applied to the skin, the latter is from about one to about thirty times the weight of the former, preferably from about one to about five times. Thus, on the first pad, the selected antibiotic should be
35 present at a level ranging from 0.5% to 5.0% w/w of the

total composition absorbed into the pad, and, on the second pad, the selected peroxide should be present at a level ranging from 1.0% to 30% w/w of the total composition absorbed into the pad. A preferred concentration is about 2% to about 3% of the selected antibiotic and about 5% to about 10% of the selected peroxide, based on the total weight of each of the compositions which are used to impregnate the pads.

10 Aqueous Emollient Peroxide-Containing Gels

A preferred peroxide-containing composition for use on one of the pads of the present applicator system comprises an effective anti-acne amount (about 1-10%, preferably about 2.5-7.5%) of an organic peroxide, preferably benzoyl peroxide in combination with an aqueous gel comprising water (about 40-75%), an effective amount (about 0.25-5%) of an inorganic gelling agent, an inorganic emollient oil plus an emollient organic ester (2.5-10%) and, optionally, an amphoteric surfactant (0.025-0.25%) and a water-miscible organic solvent, i.e., 10-20% of a (C₂-C₄) alkanol.

Emollient Oils. Useful emollient oils for incorporation into the aqueous reactant phase include those water-insoluble liquids which can function to soften the skin of the user and provide a degree of barrier protection against environmental irritants.

Preferred emollients oils for use in the present invention include mixtures of (i) inorganic emollient oils (minerals or silicone oils) with (ii) emollient organic esters. Mineral oils are complex mixtures of paraffin and naphthalene hydrocarbons, e.g., the C₁₈-C₃₆ hydrocarbon mixtures available from Penreco, Butler, PA, e.g., Penetec® technical mineral oil (viscosity 3.4-4.7 centistokes @40°C), the Drakeol® light mineral oils, USP (viscosities 6.5-30.2

centistokes @40°C) and the Drakeol® mineral oils, USP (viscosities 35.0-70.0 @40°C). The specific gravity of mineral oils useful in the practice of the present invention preferably is about 0.80-0.9 at 15.6°C (60°F). Preferred 5 mineral oils for use in the present vehicles are odorless, colorless (30+Saybolt color) and comply with FDA requirements under the Federal Food, Drug and Cosmetic Act.

Silicone fluids can also be used alone or in combination with the mineral oil component. Useful classes 10 of silicone fluids include the linear polydimethylsiloxanes or the tetrameric or pentameric cyclic siloxanes (cyclomethicones) which are available from Rhone-Poulenc, Inc. (Monmouth Junction, N.J.) as the Rhodorsil® fluid series in a wide range of viscosities (i.e., 10-10,000 15 cps.). Fluids of about 0.5-150 cps viscosity, preferably about 25-100 cps, are preferred. Preferably, mineral oil and/or silicone oils will make up about 0.1-1% of the peroxide-containing gelled vehicle.

Preferred emollient esters include those organic 20 esters that can also function as nonionic surfactants. They include about 0.5-5% of (polyoxyethylene) ((C₈-C₁₂) fatty acid) esters of glycerol, such as PEG-7 glyceryl cocoate (Cetiol® HE, Henkel), PEG-30 glyceryl cocoate, PEG-12 glyceryl laurate, PEG-20 glyceryl oleate, and the like, 25 wherein the number designates the approximate number of oxyethylene moieties present.

Another preferred class of emollient esters are the polyoxypropylene, polyoxyethylene ethers of lanolin or of (C₈-C₂₂) fatty alcohols, such as PP5-5-Ceteth-20 which is 30 the ether of cetyl alcohol having 20 ethylenoxy units and 5 propylenoxy units (Procetyl® AWS, Croda), and Lanexol® AWS (PPG-12-PEG-50 lanolin, Croda). These mixed polyalkylenoxy ethers may be present at about 0.1-0.5% of the total peroxide-containing gelled vehicle.

Other useful emollient esters include (C₅-C₃₀)-alkyl, (C₈-C₂₂)fatty acid esters, wherein the fatty acid moiety is optionally substituted with a (C₈-C₂₂)alkanoyl group. Such esters are commercially available, e.g., as 5 Ceraphyll[®] 847 [2-octyl(dodecyl)] (12-steroyl-stearate), Ceraphyll[®] 368 (2-ethylhexylpalmitate) and Ceraphyll[®] 230 (isocetyl stearate) from Van Dyk & Co., Belleville, N.J. Preferably, the aqueous reactant phase will include about 5-50% by weight of these fatty acid esters, most preferably 10 about 10-45%.

Other useful classes of water-insoluble emollient esters include the (C₈-C₂₂)fatty acid esters of propylene glycol, e.g., propylene glycol dicaprylate/dicaprate (Edenol[®] 302); the (C₆-C₁₂)fatty alcohol esters of hydroxy 15 (C₈-C₂₂)fatty acids, e.g., octylhydroxy stearate (Naturechem[®] DHS); the esters of fatty alcohol(polyethylene oxideethers) with fatty acids, e.g., myreth-3-caprate, myreth-3-myristate and myeth-3-myristate (Cetiol[®]1414-E, Henkel), wherein the number indicates the number of oxyethylene moieties present; 20 the benzyl alcohol esters of one or more C₁₀-C₂₀ fatty acids, e.g., benzyl linoleate (Dermol[®] 618, Alzo, Inc., Matawan, NJ); the fatty alcohol esters of benzoic acids such as the C₁₂-C₁₅ alkylbenzoates (Finsolv[®] TN, Finetex, Inc.) described in U.S. Patent Nos. 4,278,655 and 4,275,222; the liquid 25 fatty alcohol esters of C₃-C₆ aliphatic carboxylic acids, i.e., isodecyl neopentanoate (Dermol[®] 105); and the (C₁-C₅)alkanol di- or triesters of dimer or trimer acid (the dimer or trimer of oleic acid). Such esters are commercially available as Schercemol[®] TT (triisopropyl trimerate) 30 and Schercemol[®] DID (diisopropyl dimerate, Scher Chemicals, Clifton, NJ). The liquid fatty acid-esters of dimer acid may also be successfully employed in the present compositions, e.g., the diisostearyl ester of dimer acid, Schercemol[®] DISD.

Surfactants. Surfactants may also be used to stabilize the gelled composition. A preferred class of these materials is fatty acid amides such as the mono- and dialkanolamides of C₈-C₂₂ fatty acids, e.g., a mono- or di(C₂-C₄)alkanol-amide.

- 5 Commercially available, nonionic surfactants of this class include lauramide DEA (Standamid™ LP, Henkel), lauramide MEA (Monamid™ LMA, Mona), lauramide MIPA (Monamid™ LIPA, Mona), myristamide MEA, myristamide MIPA, Myristamide DEA, Oleamide DEA, oleamide MEA, oleamide MIPA, cocamide MEA, cocamide
10 DEA, cocamide MIPA, stearamide MEA, stearamide MIPA, stearamide DEA and the like.

- Other useful nonionic surfactants include the amine oxides, such as the C₁₀-C₂₀-alkyl-di(lower)alkyl-amine oxides or the [C₁₀-C₂₀-alkylamido, (C₂-C₅)alkyl]di(lower)-
15 alkyl-amine oxides. Especially preferred members of this class include lauryl(dimethyl) amine oxide, myristyl(dimethyl)amine oxide, stearyl(dimethyl)amine oxide (Schercamox™ DMS, Scher Chemicals, Inc., Clifton, NJ); coco(bis-hydroxyethyl)amine oxide (Schercamox™ CMS),
20 tallow(bis-hydroxyethyl)amine oxide and cocoamidopropyl(dimethyl)amine oxide (Schercamox® C-AA).

- A further useful class of surfactants is the anionic surfactants, including the C₁₄-C₁₈ primary alkyl sulfates, such as sodium lauryl sulfate, sodium cetyl
25 sulfate and sodium stearyl sulfate.

- Gelling Agents. The present peroxide-containing vehicles will comprise an amount of an inorganic or organic gelling agent effective to gel or thicken the aqueous-alcoholic
30 mixture to at least a cream- or lotion-like consistency.

Preferably, the inorganic gelling agents employed will comprise those of natural or synthetic of mineral origin. Preferred gelling agents are the montmorillonite clays such as the saponites, hectorites, laponites and the 5 montmorillonite colloidal clays such as Veegum™ (Vanderbilt Minerals, Murray, KY) or Magnabrite™ (American Celloid Co., Skokie, IL). Clay-based gellants containing montmorillonite and aluminum hydrosilicate together with suborganic radicals are available as the Tixogel™ series (United Catalysts, 10 Louisville, KY). A useful montmorillonite clay gelling agent is a bentonite such as Korthix™ H (Kaopolite, Inc., Union, NJ). Inosilicates can also be used, alone or in combination, with the clays. Preferred inosilicates are the naturally-occurring calcium metasilicates such as 15 wollastonite, available as the NYAD™ wollastonite series (Processed Minerals Inc., Willsboro, NY). Synthetic sodium magnesium silicate clays, alumina, magnesium aluminum silicate, and fumed silicas can also be used as gelling agents.

Useful organic gelling agents include microcrys- 20 talline cellulose and hydroxyalkyl cellulose ethers such as hydroxypropylmethyl cellulose (HPMC), hydroxymethyl cellulose (HMC), carboxymethyl cellulose (CMC), 2-hydroxyethyl cellulose, 2-hydroxyethylmethyl cellulose, and 2-hydroxypropyl cellulose (Klucel® H).

25 Organic gelling agents useful in the practice of the present invention also include polyvinylpyrrolidone and polymeric organic waxes. The useful polymeric waxes include ethylene acrylate copolymers, ethylene acrylic acid copolymers and polyethylene (e.g., oxidized polyethylenes). 30 These materials are commercially available in the form of aqueous emulsions or dispersions, e.g., from Allied Chemical, Morristown, NJ, as the A-C Copolymer and A-C Polyethylene series, such as A-C Copolymer 540, A-C Copolymer 580 and A-C Polyethylene 617 and 629. Waxy 35 polyethylene glycols (PEG) such as those of a molecular

weight of about 800 to 1700-2000 are preferred for use in the present gels.

Preferred gelling agents include the so-called hydroxylated vinylic polymers, particularly those disclosed in U.S. Patent No. 2,798,053. Among those hydroxylated vinylic polymers of special interest herein are described generally as interpolymers of a monomeric monoolefinic acrylic acid, and from about 0.1% to about 10% by weight based on the total monomer of a monomeric polyether of an oligosaccharide in which the hydroxyl groups which are modified are esterified with allyl groups with said polyether containing at least two allyl ether groups per oligosaccharide molecule. Commercially available interpolymers of this type are marketed under the trade name Carbopols®. These are described as being polymers of acrylic acid cross-lined with about 1% of a polyallyl ether of sucrose having an average of 5.8 allyl groups for each sucrose molecule. These polymers have molecular weight in the order of magnitude of 1,000,000. Such polymers are available from the B.F. Goodrich Chemical Company and are sold under such trademarks as Carbopol® 934, Carbopol® 940, Carbopol® 941 and Carbopol® 934P.

The quantity of gelling agent that may be contained in the present compositions may also vary somewhat. Ordinarily, this will constitute about 0.1% to about 15% by weight, and preferably about 0.5% to about 3% by weight, based on the total weight of the finished peroxide-containing vehicle.

A typical formulation for an aqueous-alcohol emollient benzoyl peroxide gel is given in Table I, below. The gel contains 15% isopropanol and 5% benzoyl peroxide, and has the consistency of a light gel.

TABLE I

<u>INGREDIENTS</u>	<u>CTFA CHEMICAL NAME*</u>	<u>%</u>
Water, distilled	-	63.73
Laponite XLS	Sodium Lithium Magnesium Silicate	1.97
Isopropanol	Isopropyl Alcohol	15.00
Cetiol HE	PEG-7 Glyceryl Cocoate	1.45
Edenol 302	Propylene Glycol Dicaprylate/- Dicaprinate	.43
Schercemol DISD	Diisostearyl Dilinoleate	.65
Naturechem OHS	Octyl Hydroxystearate	.95
Finsolv TN	C12-15 Alcohols Benzoate	.70
Cetiol 1414-E	Myreth-3 Myristate	.16
Lamapon S	Potassium Coco-Hydrolyzed Animal Protein	.05
Procetyl AWS	PPG-5-Ceteth-20	.15
Lanexol AWS	PPG-12-PEG-50 Lanolin	.15
Mineral Oil Light	Mineral Oil	.25
Schercamox C-AA	Cocamidopropylamine Oxide	.06
Benzoyl Peroxide (35%)	-	<u>14.30</u>
		100.00

* See CTFA Cosmetic Ingredient Dictionary, N.F. Estrin, ed., The Cosmetic, Toiletry and Fragrance Association, Inc., pub., Washington, D.C. (3d ed. 1982).

To prepare this formulation, the laponite is added to the water with vigorous stirring. In another vessel, the emollient oils and the amine oxide are added in the order listed with stirring, and the mixture is heated gradually to 60°C, then cooled to 25°C. The isopropanol is then added to

the water-laponite stirring with good agitation, and the resultant mixture is stirred into the emollient mixture, followed by the addition of benzoyl peroxide.

5 Aqueous, Non-Emollient Peroxide Gels

The complex mixture of emollient esters and surfactants listed in Table I is not essential to the preparation of an aqueous benzoyl peroxide-containing acne treatment gel. For example, 10-20% benzoyl peroxide can be
10 stably dispersed in about 50-80% water with the aid of an effective amount of one or more inorganic gelling agents, such as those useful to prepare the emollient gels above. Preferably, about 0.5-25%, most preferably about 2-20%, of total gelling agent will be used. Typical formulations for
15 four such gels are provided in Table II, below.

TABLE II

<u>INGREDIENTS</u>	<u>CTFA CHEMICAL NAME</u>	<u>Formulation</u>			
		<u>A</u> <u>%</u>	<u>B</u> <u>%</u>	<u>C</u> <u>%</u>	<u>D</u> <u>%</u>
Water	---	66.50	83.13	83.38	73.04
Laponite XLS	Sodium Lithium Magnesium Silicate	2.06	-	-	1.80
Laponite XLG	Sodium Lithium Magnesium Silicate	-	2.57	1.81	.46
Veegum HV	Magnesium Aluminum Silicate	-	-	0.51	-
Dispal Alumina 23N4-20 Sol.	Aluminum Oxide Dispersion	17.14	-	-	-
Dispal Alumina 23N4-80 Powder	Aluminum Oxide	-	-	-	10.40
Benzoyl Peroxide (35%)	---	<u>14.30</u>	<u>14.30</u>	<u>14.30</u>	<u>14.30</u>
Total		100.00	100.00	100.00	100.00

Gels A, B and D are thick/viscous gels. Gel C is thixotropic, in that it fluidizes when subjected to shear.

Anhydrous Emollient Peroxide Gel

5 The benzoyl peroxide gel component of the present invention can also be prepared by dispersing the benzoyl peroxide in an essentially water-alcohol free blend of surfactants, along with about 1-10% of the inorganic gelling agent. Such gels can comprise about 75-90% of a mixture of
10 inorganic and organic emollient oils, about 1-10% peroxide and, optionally, above 0.1-1% of amine oxide or other amphoteric surfactant. The inorganic oil is preferably a minor proportion, i.e., about 1-7.5% of the finished gel. A

typical formulation for such a gel is given in Table III below.

TABLE III

<u>INGREDIENTS</u>	<u>CTFA CHEMICAL NAME*</u>	<u>%</u>
Cetiol HE	PEG-7 Glyceryl Cocoate	23.64
Edenol 302	Propylene Glycol Dicaprylate/Dicaprate	7.01
Schercemol DISD	Diisostearyl Dilinoleate	10.51
Naturechem OHS	Octyl Hydroxystearate	15.49
Finsolv TN	C12-15 Alcohols Benzoate	12.80
Cetiol 1414-E	Myreth-3 Myristate	2.61
Lamapon S	Potassium Coco-Hydrolyzed Animal Protein	0.81
Procetyl AWS	PPG-5-Ceteth-20	4.07
Mineral Oil Light	Mineral Oil	4.07
Schercamox C-AA	Cocamidopropylamine Oxide	0.49
Cabosil M-5	Amorphous Silica	4.20
Benzoyl Peroxide (35%)	-	<u>14.30</u>
Total		100.00

These gels are "anhydrous" in the sense that the only water or alcohol present is provided via the commercially available forms of the emollient esters and surfactants, and is preferably $\leq 5\%$ of the total gel.

Antibiotic Compositions Acne Treatment

Preferred dual pad applicators intended for acne treatment will comprise a pad having an absorbed aqueous, alcoholic, or aqueous-alcoholic solution of the antibiotic, of which erythromycin, tetracycline, clindamycin and the pharmaceutically acceptable salts thereof are preferred. Useful salts include the salts of inorganic or organic acids, such as the hydrochloride, phosphate, glyconate, citrate, maleate, stearate, and hydrobromide salts. Useful alcohols include ethanol, isopropanol and mixtures thereof. Benzyl alcohol and/or butanol can also be used in combination with varying amounts of water. All, or a part of the alcohol, can be replaced by other volatile water-miscible organic solvents such as m-pyrol, liquid polyethylene glycols, acetone, THFA and the like.

The antibiotic or salt thereof will preferably be dissolved or dispersed in the solvent or solvent system at a concentration effective to significantly decrease the skin concentration of Corynebacterium acnes upon topical application of about 0.5-5.0 mls of the antibiotic solution for the skin of the afflicted human or animal, e.g., an about 0.5%-5% solution or dispersion of the antibiotic in the solvent or solvent system is preferred.

Emollient organic esters are preferably also self-emulsified into an aqueous alcohol system, e.g., one comprising about 80-95% aqueous alcohol, about 5-15% emollient organic ester, and about 0.1-5% antibiotic, in order to provide the pad with a better skin-feel and to aid in the even distribution of the antibiotic on the skin. A typical emollient formulation comprising 1.0% clindamycin phosphate, is given in Table IV, below.

TABLE IV

<u>Ingredient</u>	<u>Percent</u>
Water	20.0
Isopropanol	70.3
10% NaOH	0.7
Clindamycin phosphate	1.0
<u>Emollient Esters</u>	
Cetiol HE	2.3
Myritol 318*	0.7
Naturechem GTR**	1.5
Finsolv TN	2.8
Cetiol 144-E	0.3
Procetyl AWS	0.5

* Caprylic/Capric Triglyceride

** Glyceryl triacetyl ricinoleate

To prepare this formulation, clindamycin phosphate is dissolved in the water at 25°C and isopropyl alcohol added, this solution is added to a preformed blend of the emollient esters and the pH of the mixture is adjusted to 5 6.8 with 10% NaOH.

Erythromycin can replace clindamycin in this formulation.

Salicylic Acid Compositions for Acne Treatment

10 In dual pad applicator packs intended for acne treatment, the antibiotic or benzoyl peroxide composition can be replaced with a composition containing salicylic acid, which acts as an antiseptic, an antifungal and a topical keratolytic agent. A suitable vehicle for salicylic

acid can be prepared by mixing water with a gelling agent and adding a water-miscible organic solvent in a weight ratio of about 0.1-4 parts water to 1.0 part solvent, e.g., a (C₂-C₄)alkanol. The salicylic acid is dispersed in this mixture at about 0.5-10% of the finished composition. Two typical salicylic acid formulations are given in Table V, below.

TABLE V

<u>Ingredients</u>	<u>CTFA Chemical Name</u>	<u>A %</u>	<u>B %</u>
Water, distilled	-	74.57	12.62
Klucel H	Hydroxypropylcellulose	1.52	-
Carbopol 934P NF	Carbomer	-	1.95
Isopropanol	Isopropyl Alcohol	21.74	82.52
Salicylic Acid Powder U.S.P.	-	<u>2.17</u>	<u>2.91</u>
Total		100.00	100.00

Formulation B yielded a light, fluid gel that spread into an even film. Formulation A yielded a thicker, fluid gel.

Retinoic Acid Compositions for Acne Treatment

As disclosed hereinabove, for the topical treatment of acne using the present dispensing and applicator system, one of the pads can be impregnated with a liquid, semi-liquid or gelled formulation comprising an effective anti-acne amount of retinoic acid, while the other pad or pads preferably contain an emollient composition to

counteract the drying/scaling properties of the retinoic acid, and/or an effective amount of a sunscreen composition to protect the user from retinoic acid-induced sensitivity to UV light.

5 Useful retinoic acid compositions can be formulated as creams, gels, or liquids; preferably comprising about 0.01-0.25 wt-% of retinoic acid. Useful gels can be formed in aqueous, water-miscible organic solvent vehicles comprising water:solvent ratios of about
10 9:1 to 1:9, in combination with an effective amount of an organic and/or inorganic gelling agent, of the classes described hereinabove. Retinoic acid-containing liquids can simply be prepared by dissolving an effective amount of
15 retinoic acid in water organic solvent, using nontoxic organic solvents, such as the (C₂-C₄)alkanols and liquid polyoxyethylene glycols disclosed hereinabove. Due to the unstable nature of retinoic acid, minor but effective amounts of antioxidants, such as BHT, are preferably included in these formulations.

20

Skin Moisturizing Composition/Sunscreens

Emollient compositions which soften and protect the skin are preferably used in conjunction with a dermatological composition comprising retinoic acid, or as a
25 carrier vehicle for retinoic acid. When used in conjunction with retinoic acid, the emollient compositions preferably include an effective amount, i.e., 1-10 wt-% of one or more, i.e., 1-3 sunscreen compounds. These include oxybenzone, ethyldihydroxypropyl-p-amino benzoate, octyl dimethyl-p-
30 aminobenzoate, para-aminobenzoic acid, and the like. Useful emollient compositions include those disclosed in Smith et al. (U.S. Patent No. 4,559,157) which are oil-in-water emulsions comprising an oil phase containing at least one emollient oil and at least one emollient wax stabilizer,
35 dispersed in an aqueous phase comprising at least one

polyhydric alcohol emollient and at least one amphoteric (amine oxide) or anionic surfactant. Effective amounts of bactericidal preservatives and fragrance may also be employed in the impregnating emulsion. These emulsions are
5 formulated so that an effective amount of emollients and fragrance is released and evenly coated onto the skin with no "skipping" or separation when the impregnated pad is pressed or rubbed against a moist skin surface. This requires that the emulsion be formulated so that it will be
10 stable and not break when mixed with the additional water present on the skin due to bathing, showering or the like.

It has been found that emollient emulsions stable under these conditions can be formulated by dispersing an oil phase comprising one or more emollient oils and one or
15 more emollient wax stabilizers in an aqueous phase comprising one or more polyhydric alcohol emollients and one or more water-soluble organic surfactants.

Therefore, the emulsions of the present invention preferably will comprise about 15-50% of water-insoluble or
20 soluble active ingredients, i.e., the emollients, surfactants, fragrance and preservatives; and 50-85% water, preferably distilled or deionized water. About 7-20% of the active ingredients will be present as the oil phase of the emulsion, while the remainder of the active ingredients will
25 be fully soluble in the water phase. Emollients will preferably comprise about 10-50% by weight of the emulsions. Emollients useful in the practice of the present invention are generally described by G. Barnet, *Emollient Creams and Lotions*, and by S.J. Strianze, *Hand Creams and Lotions*, in
30 *Cosmetics--Science and Technology*, Wiley Interscience Pub. (1957) at pages 99-181.

Emollient Wax Stabilizer. The emollient oils useful in these compositions have been described hereinabove.

Emollient wax stabilizers are waxy solids at room
35 temperature. They function to soften and smooth the skin

surface and to prevent evaporation of interior skin moisture. They also can function as nonionic emulsifying agents and act to adjust the final viscosity of the composition. The emollient wax stabilizers useful in the practice of the present invention include beeswax, spermaceti, solid hydrocarbons, C_{12} - C_{18} fatty alcohols, glyceryl monostearate, ethylene glycol monostearate, polyethylene glycol distearate and other (C_{12} - C_{18}) fatty acid- (C_2 - C_5) polyol esters. Particularly useful in the practice of the present invention are the fatty alcohols, such as lauryl, cetyl, oleyl and stearyl alcohols or mixtures thereof, and the fatty acid-polyol esters, i.e., glyceryl monostearate, which is commercially available as Cerasynt[®] Q from Van Dyk & Co., Belleville, NJ. In one class of emulsions useful in the practice of the present invention, all or a part of the emollient oil, isostearyl neopentanoate, or Ceraphyll[®] 375, is replaced with one of the emollient waxes of the Softisan[®] Series (Dynamit Nobel Chemicals, Rockleigh, NJ), a fragrant emollient ester of the class of compounds designated as triglycerides of C_{10} - C_{18} saturated fatty acids, which allows the use of less fragrance, thus resulting in a cost savings. An especially useful member of this series is Softisan[®] 100. Preferably, emollient waxes will make up about 3-10% of the composition, most preferably about 3.5-8%.

Polyhydric Alcohol Emollient. The emulsions of the present invention will also include one or more polyhydric alcohol emollients which are preferably C_2 - C_5 alkanols substituted with 2-4 hydroxyl groups, such as propylene glycol, glycerol, and sorbitol. Polyhydric alcohol emollients will preferably make up 5-15% by weight of the emulsion. One especially preferred mixture of polyhydric alcohol emollients is an about 1:1 mixture of propylene glycol and glycerol.

Therefore, preferred emulsions useful in the present invention may be formulated so as to contain about 50-85% water, about 4-12% emollient oil, about 3.0-10% emollient wax stabilizer, about 5-20% polyhydric alcohol 5 emollient, and about 0.5%-10% organic, water-soluble surfactant, and optionally, about 0.025-0.75% antibacterial preservative and about 0.1 to 0.5% fragrance.

The following ingredients were combined in the weight percentages indicated in Table VI to form a 10 moisturizing composition by the procedure described below.

TABLE VI

<u>INGREDIENT</u>	<u>PERCENT</u>	<u>GRAMS</u>
<u>Group A</u>		
Glyceryl Monostearate	5.0	750.0
Cetyl Alcohol	0.5	75.0
Mineral Oil	5.0	750.0
i-Stearyl Neopentanoate	3.0	450.0
Propyl Parabens	0.10	15.0
Butyl Parabens	0.05	7.5
<u>Group B</u>		
Water (deionized)	62.15	9,322.5
Methyl Parabens	0.30	45.0
Propylene Glycol	5.00	750.0
Glycerol	5.00	750.0
Lauryl Dimethyl Amine Oxide (29-31% Solution in H ₂ O)	3.0	450.0
<u>Group C</u>		
Water	5.0	750.0
Sodium Lauryl Sulfate	0.50	75.0
Fragrance	0.30	45.0
Water	5.0	750.0
Kathon CG (Preservative)	<u>0.10</u>	<u>15.0</u>
	100.00	15,000.0

The oil-phase ingredients of Group A were mixed and heated to 75°C. The water-phase Group B ingredients were separately mixed, heated to 75°C and then the Group A ingredients were added with good agitation. Stirring was 5 contained for 10 minutes and a 23°C solution of the Group C ingredients was added subsurface to the stirred 72°C mixture. The emulsion was stirred and cooled to 45°C at which point the fragrance was added. The mixture was stirred until its temperature fell to 35°C. The mixture was 10 allowed to stand overnight and then the preservative solution was added with stirring. The mixture was stirred for 45 minutes and then used to impregnate a sheet of Crown Textile C-785 (1.25 oz/yd²) via a Meyer Rod to form a one-use cosmetic applicator pad (0.25 g per 1.5 square inches of 15 fabric).

The resultant applicator pads were moist but not sticky or unduly wet to the touch and readily applied a clear, non-sticky, homogenous film of the emollient emulsion to dry skin surfaces. The film retained these desirable 20 characteristics when the skin was moistened prior to use of the applicator. As noted above, an effective anti-acne amount of retinoic acid can optionally be combined with this emollient composition.

25 Make-Up Remover Compositions

The present applicator system can also be used as a dual system applicator wherein one or more pads are used to apply one or more of the pigment-containing cosmetic compositions variously known as "make-up," i.e., lipstick, 30 rouge, blush, eyeshadow, eyeliner and the like, while another of the pad or pads is impregnated with a composition that will remove the make-up, e.g., will solubilize the waxy components, or waxy base, of the make-up and cause it to be absorbed by the porous applicator pad.

A preferred make-up remover composition is disclosed in Kellett (U.S. Patent No. 4,806,572) and comprises a wax-free mixture of about 25-75% water, about 15-70% of a water-insoluble liquid emollient oil (as 5 described hereinabove) and an amount of surfactant (about 1-15%) effective to stabilize the aqueous phase as a homogeneous emulsion. Preferred emollient oils comprise a mixture of a mineral oil and a liquid fatty acid ester, i.e., a (C₅-C₃₀)alkyl(C₈-C₁₂)fatty acid ester. Preferably, 10 the surfactant is a mixture of an anionic surfactant with a nonionic polyoxyalkylene block copolymer (mw 1500-3500) in a weight ratio of about 1.5-0.75:1.

Preferred make-up remover pads comprise a resilient open-celled, hydrophilic polyurethane foam matrix, 15 wherein said matrix integrally incorporates an aqueous phase incorporating about 25-75% water, about 15-70% of a water-insoluble liquid emollient oil, and an amount of surfactant effective to stabilize the aqueous phase so that it is released from the foam matrix as a homogenous emulsion when 20 the pad is applied to skin, and wherein said aqueous phase contains no natural or synthetic wax.

Steroid Compositions

To treat skin irritations and other dermatological 25 conditions such as various dematoses, including chronic neurodermatitis, nummular dermatitis, atopic dermatitis, and psoriasis; eczema, poison plant rashes, insect bites and rashes due to cosmetics, detergents, jewelry and the like, one or more of the pads of the present applicators can be 30 impregnated with an effective dermatological amount of one or more steroids, such as a corticosteroid. The pad may be impregnated with a dry powder of the steroid or steroids, optionally in combination with a solid inert carrier such as starch, talcum powder, dextrin, microcrystalline cellulose 35 and the like. Preferably, the steroid is impregnated into

the pad in combination with a pharmaceutically acceptable carrier, i.e., in combination with a suitable solvent or solvent mixture (in solution), a liquid lotion or emulsion, or an ointment or a gel.

5 The percentage of the steroid present in the vehicle can be varied widely, depending on the potency of the steroid with respect to the condition to be treated, but can range from about 0.025-0.05% in the case of corticosteroids such as betamethasone dipropionate or
10 fluocinonide, up to as much as 1-5% in the case of hydrocortisone or cortisol.

Useful corticosteroids, their dermatological indications and dosages are disclosed in Remington's Pharmaceutical Sciences, A. Osol, ed., Mack Publishing,
15 Easton, PA (16th ed. 1980) at pages 898-912, which is incorporated by reference herein, and include betamethasone, cortisol, dexamethasone, flumethasone fluocinolone, fluorometholone, flurandrenolide, methylprednisolone, prenisolone, desoximetasone, diflorasone, triamcinolone, and
20 their nontoxic organic acid salts such as the benzoate, acetate, valerate, pivalate, acetonide, acetonide-acetate, diacetate, butyrate, dipropionate and valerate salts, and the like.

In combination with the appropriate carrier, if
25 any, the steroid will be impregnated into the applicator pad so that, upon application of the pad to the afflicted skin area, an effective amount of steroid will be delivered to the skin, e.g., from about 500 μ g-250 mg of total steroid per m^2 of skin, depending upon the steroid or steroids
30 present in the composition.

Two representative steroid-containing solutions comprising mixtures of organic solvents as the carrier vehicle are given in Table VII below.

Table VII. Steroid Solutions

<u>Ingredient</u>	<u>Formulation (wt-%)</u>	
	<u>A</u>	<u>B</u>
Propylene glycol	86.18	82.95
Isopropyl alcohol	12.00	7.00
m-Pyrrol	1.75	-----
Carbitol	-----	10.00
Betamethasone dipropionate	0.64	-----
Fluocinonide (Lidex™)	-----	0.05

The steroid can also be microencapsulated or stabilized by absorption onto or into dextrin or cyclodextrin particles by methods known to the art.

As noted above, when a steroid-containing composition is included in one of the pads, the other pad or pads can contain dermatological agents which complement or enhance the activity of the steroid. Such ingredients include antihistamines, antibiotics, e.g., in combination with the carrier vehicles described above, emollient compositions such as those disclosed above, anti-fungal agents, sunscreens as disclosed above, and compositions which will enhance penetration of the steroid into the skin. The latter compositions include those which, following their application, form an occlusive barrier or film over the applied film of steroid-containing composition. Such barrier-forming compositions include those which comprise solvent-dissolved or dispersed film-forming polymers such as polysaccharides, polyvinyl alcohols, polyacrylate salts, and/or cross-linked polyacrylate hydrogels.

Occlusive/Semi-Occlusive Film-forming Compositions

To enhance the effect of a steroid or other
therapeutical agent on the skin, it is desirable to have a
moisturizing or emollient effect to supplement the curative
5 action of the agent. Also, it is also preferred that an
occlusive barrier be applied to the skin during application
to enhance the retention and the bioavailability of the
therapeutical agent.

Current dermatological treatments apply an
10 appropriate amount of a cream or ointment containing the
steroid or other therapeutical agent to the skin, and then
cover the affected area with a piece of plastic film, gauze,
band-aid, or other like covering, to provide a barrier to
occlude the skin and facilitate the retention of moisture on
15 the skin surface. A commonly used plastic film is composed
of a polyvinylidene chloride (PVDC) copolymer and marketed
under the trademark Saran[®]. This way of occluding the
surface of the skin, however, is difficult to administer and
inconvenient to the patient. It would be desirable,
20 therefore, to administer a therapeutical agent to the skin
in a emollient system while simultaneously forming an
occlusive or semi-occlusive barrier on the surface of the
skin. Such a system would enhance penetration of a
therapeutic agent into the skin and provide a moisturizing
25 action.

To this end, the applicator system may be used as
a dual system applicator for administering a film-forming
composition containing a therapeutical agent, in which one
of the pads is impregnated with an aqueous, alcoholic or
30 aqueous alcohol solution formulated with a film-forming, or
barrier, polymer and an effective amount of the therapeutic
agent, while the other pad or pads contain an emollient
solution, as described hereinabove for the topical treatment
of acne and dermatological conditions.

Each of the solutions are coated onto separate applicator pads which should be moist but not unduly wet to the touch. The solutions are dispensed and mixed together by rubbing over the diseased or irritated portion of the skin, and allowed to dry to a film on the surface of the skin. The solutions are applied to the skin sequentially or simultaneously and mixed together in situ. When combined on the skin, the solutions form a plasticized film which provides an occlusive or semi-occlusive barrier on the skin. The film retains the therapeutical agent in intimate contact with the skin, enhances penetration of the therapeutical agent transdermally into the skin, and may act to release the therapeutical agent on a controlled basis over time. The film is maintained on the skin surface for a predetermined period of time effective to deliver the therapeutical agent to the skin to provide the desired treatment of the skin disorder. The solutions may include an inorganic or organic gelling agent, one or more surfactants, preservatives and/or fragrance, also as described hereinabove. A penetration enhancing agent may also be included in one or both of the solutions.

The emollient system provides a moisturizing and soothing effect on the skin, and the occlusive/semi-occlusive nature of the film prevents water evaporation so that the skin becomes hydrated to facilitate and enhance penetration of the drug transdermally into the skin. The solutions may be applied to a moist skin surface, as for example, after showering or bathing when the skin is fully hydrated. The barrier compositions are useful for treating skin disorders or diseases such as psoriasis, eczema, atopic dermatitis, alopecia areata, warts, keratoses, acne, and the like.

Polymer solution. In a dual pad applicator, at least one pad will have an absorbed aqueous, alcoholic, or aqueous-alcoholic solution of the barrier polymer. Useful alcohols include ethanol, isopropanol and mixtures thereof. Benzyl alcohol and/or butanol can also be used in combination with varying amounts of water. All, or a part of the alcohol, can be replaced by other volatile water-miscible organic solvents such as m-pyrol, liquid polyethylene glycols, acetone, THFA and the like. An amount of an organic solvent (i.e., alcohol, glycol, and the like) may be included in an aqueous solution to dilute the polymer in solution, to aid in drug solubilization, enhance film formation, and increase skin penetration of the therapeutical agent transdermally. The polymer solution preferably includes about 15-50 wt-% of the barrier polymer and about 50-85 wt-% solvent.

The barrier polymer may be a water-soluble or water-dispersible polymer. Examples of such polymers include polyvinylpyrrolidone (PVP) (Plasdone K-29/32, GAF Corp., Wayne, NJ); alkylated vinylpyrrolidone polymers such as butylated polyvinylpyrrolidone (Ganex P-904, GAF Corp.); copolymers of vinylpyrrolidone (VP) such as VP/eicosene copolymer (Ganex V-220, GAF Corp.), VP/hexadecene copolymer (Ganex V-216, GAF Corp.), VP/vinyl acetate copolymer (PVA/VA E-335, PVA/VA E-535, PVA/VA E-735; GAF Corp.), a VP/dialkylaminoacrylate copolymer, as for example, VP/dimethylaminoethylmethacrylate copolymer (Copolymer 937, Copolymer 958, GAF Corp.); and polyquaternary polyvinylpyrrolidones such as polyquaternium-16 (Luviquat FC 370, Luviquat HM 552, BASF).

Also useful are polymers which are soluble in organic solvents. Such polymers include, for example, monobutyl esters of polyethylvinylether/maleic anhydride polymers (Gantrez ES-425, Gantrez AN-149, Gantrez S-95, GAF Corp.), polyvinylidene dichloride (PVDC) such as Saran[®] F-Resin (Dow Corning Corp., Midland, Mich.), and compound 76

RES M3-153 (Union Oil of Calif., San Francisco, Calif.). The polymer may be diluted in solution using an organic solvent such as a lower C₂-C₄ alcohol, acetone, ethyl acetate, glycol, and the like.

5 Another class of polymers that may be used are polysaccharides such as cellulose, starches, chitins, chitosans, alginates, carrageenans, agars, agaroses, locust bean gums, konjacs, and modified hydrophobes may be included alone or in combination with other polymers.

10

Emollient Phase. At least one pad is impregnated with an emollient solution which is combinable with the polymer phase to aid in the even distribution of the therapeutical agent and the barrier polymer on the skin to form an
15 occlusive or semi-occlusive film. The emollients generally function to soften and lubricate the skin surface and to prevent evaporative loss of skin moisture supplied by underlying tissues. The emollients also function to provide a protective barrier against environmental irritants.

20

The emollient solution contains one or more emollient oils as described hereinabove. Preferred emollient oils include mineral oil, fatty alcohol esters such as C₁₂-C₁₅ alkylbenzoates (Finsolv TN), glycols such as polypropylene glycol and glycerol (water-soluble),
25 polyethoxylated soya sterols from the Generol[®] 122 series (Generol 122E-25, Generol 122E-10 and Generol 122 (mix)) (Henkel Corp., Ambler, PA), mixed polyalkylenoxy ethers such as polyoxypropylene, polyoxyethylene ethers of lanolin or of (C₈-C₂₂) fatty alcohols (Procetyl[®] AWS, Croda), and the like.
30 The emollient oil may be a mixture of an inorganic emollient oil (mineral or silicone oils) with an emollient organic ester, as described hereinabove.

The liquid emollients are preferably self-emulsified into an aqueous alcohol system, such as one comprising about 50-95% aqueous C₂-C₄ alcohol such as ethanol, isopropanol and the like, or a water-miscible solvent such as m-pyrol, glycol ether, liquid polyethylene glycol, acetone, n-methyl-2-pyrrolidone, and the like, and about 5-50% emollient oil. The emollient solution may also include all or part of the therapeutical agent.

- 10 Therapeutical Agent. An effective amount of the therapeutical agent is included in the polymer solution and/or the emollient solution, such that when the solutions are combined on the skin, the agent is applied in an amount effective to provide topical and/or transdermal treatment of the relevant skin disease or disorder. Although it is preferred that the therapeutical agent is included in the polymer solution, all or part of the therapeutical agent may be included in the emollient phase of the composition. An about 0.5-5% solution or dispersion of the therapeutical agent in the solvent or solvent system, is preferred.

A wide variety of therapeutical agents are useful in the present compositions. Particularly useful therapeutical agents include, for example, analgesics, anti-inflammatory agents and topical antipruritics (anti-itch), as for example, non-steroids such as acetaminophen, aspirin, camphor, bufexamac, ibuprofen, indomethacin, and the like; and steroids such as hydrocortisone, hydrocortisone acetate, hydrocortisone valerate, hydrocortisone butyrate, desonide, triamcinolone acetonide, betamethasone valerate, betamethasone dipropionate, betamethasone benzoate, clobetasol propionate, halcinonide, desoximethasone, amcinonide, fluocinonide, fluandrenolide, alclometasone dipropionate, fluocinolone acetonide, diflorasone diacetate, mometasone furoate, fluorometholone, clocortolone pivalate,

triamcinolone acetonide, halcinonide, and the like, and cyclodextrin complexes of these steroids.

The therapeutical agent may be dermatologically effective, such as an anti-psoriatic compound such as 5 anthralin (dithranol), coal tar extract, and the like; a keratolytic agent such as salicylic acid, urea, and the like; a local anaesthetic agent such as lidocaine, benzocaine, and the like; an anti-acne agent such as benzoyl peroxide, vitamin A derivatives, and the like; and 10 a wart removing agent such as salicylic acid, lactic acid, and the like; and other like agents.

For transdermal treatment of a skin disorder, it is preferred that the therapeutical agent possesses a molecular weight effective to allow passage of the agent 15 transdermally through the skin on a controlled basis.

Penetration Enhancing Agent. The polymer solution and/or the emollient solution may also include a penetration enhancing agent, or pharmacologically inert substance, to 20 enhance the penetration rate of a therapeutical agent through the skin. For example, a penetration enhancing agent may be included to increase the flux rate of a therapeutical agent through the skin by altering the thermodynamic activity of a penetrant or a co-solvent 25 incorporated into the film-forming composition, or to affect the partition coefficient between the therapeutical agent and the skin to promote release of the therapeutical agent from the film into the skin, and the like.

Useful penetration enhancers include, for example, 30 dimethyl sulfoxide, N,N-dimethyl acetamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, Carbitol solvent (Union Carbide), propylene carbonate, 1,5-dimethyl-2-pyrrolidone, 2-pyrrolidone-5-carboxylic acid, and the like. The solutions may include a penetration enhancing agent in an amount of 35 about 0.01-20 wt-%.

Use of the Dispensing and Applicator System. Any of the above-described compositions can be preformulated and applied to the pads, which have been preattached to the base or cover sheet, by dipping, spraying or brushing techniques 5 well known to the art.

In practice, the user, e.g., a human afflicted with acne, would either expose the medicated pads and apply them sequentially or simultaneously to the afflicted area. For example, the user might first expose a pad impregnated 10 with Retin[®] A or an anti-acne antibiotic, i.e., erythromycin or clindamycin or a pharmaceutically acceptable salt thereof, either dissolved in a non-toxic organic solvent, or dispersed in a gelled vehicle, such as that described in conjunction with Table IV, above. After applying the anti- 15 biotic pad to the afflicted skin area, the user would expose the second pad impregnated with peroxide in one of the vehicles described in conjunction with Tables I-III, above, or a pad impregnated with salicylic acid-containing vehicle. This same skin area would then be contacted with the second 20 pad, in order to combine the two active ingredients *in situ*. Alternatively, the user could expose two adjacent pads, and apply the adjacent pads essentially simultaneously to the skin, to deposit, for example, a mixture of antibiotic- and peroxide-containing vehicles thereto, preferably in a homo- 25 geneous, even film.

Each composition will be absorbed into a single pad in an amount effective to provide a unit dosage of each of the bioactive ingredients therein. It is to be understood that such a dose can vary widely, as it will be based 30 on the size of skin area to be treated, and the nature and severity of the dermatological condition to be treated. For example, the amount of a given liquid, semi-liquid or gelled composition delivered to the skin of the user may vary from as little as 0.25-0.5 g to as much as 1-3 g, depending upon 35 the choice of active ingredient, the size of pad and type of

material of which it is constructed and the skin area and condition to be treated. Thus, the amount of active ingredient delivered as a unit dose can be preselected, using the weight percentages provided hereinabove as guidelines.

5 For administering the occlusive/semi-occlusive film-forming compositions, the user would expose the pads containing the polymer solution and the emollient solution, and apply the solutions sequentially or simultaneously to mix the solutions together as a coating over the afflicted
10 area. The solutions are then allowed to dry to a film which is maintained on the skin surface for a effective time period to deliver the therapeutical agent onto the skin surface or transdermally through the skin to effect treatment of the skin disorder. For example, for treating
15 psoriasis, the user might expose a pad impregnated with a barrier polymer solution containing betamethasone dipropionate, and a pad containing the emollient solution, and apply the solutions simultaneously onto the afflicted skin area to combine the solutions *in situ* in a homogeneous,
20 even film. Alternatively, the user could expose one pad then the other, and apply each pad sequentially to the skin.

 The disclosures of all patents, patent applications and other documents cited herein are incorporated by reference. The invention has been described
25 with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. Further, the invention is not to be construed as limited to the specific
30 embodiments shown in the drawings.

WHAT IS CLAIMED IS:

1. A method for applying a plurality of dermatological agents to the skin from one dispensing and applicator system comprising the steps of:
 - (a) providing a dispensing and applicator system comprising:
 - (1) a flexible, moisture impermeable support sheet;
 - (2) a plurality of applicator pads affixed in a separated array to the surface of said support sheet; each of said pads being impregnated with a composition comprising a different dermatological agent; and
 - (3) a flexible, moisture-impermeable cover sheet having its peripheral surface releasably sealed to the opposed peripheral surface of the support sheet so as to form a compartment containing said pads and defined by a continuous seal, which seal is positioned inwardly from the edges of the sheets over a portion of the opposed peripheral surfaces, so as to form two opposed flanges, and wherein the cover sheet and the support sheet are also releasably sealed together between said pads to divide the compartment into a plurality of subcompartments, each containing one of said pads;
 - (b) manually grasping and separating the flanges to at least partially release the cover sheet from the support sheet, so that said pads are exposed; and
 - (c) contacting one or more of said pads with the skin to release the compositions sequentially or essentially simultaneously from the pads, to thereby apply a film of a mixture of the agents onto the skin.

2. The method of claim 1, wherein a first applicator pad impregnated with a first composition comprising a first dermatological agent and a second applicator pad impregnated with a second composition comprising a second dermatological agent, are affixed to one surface of said support sheet.
3. The method according to claim 1, wherein the compositions are released essentially simultaneously from the pads.
4. The method according to claim 2, wherein the first dermatological agent is an effective anti-acne amount of a peroxide.
5. The method according to claim 4, wherein the first dermatological agent comprises benzoyl peroxide.
6. The method according to claim 4, wherein the first applicator pad is impregnated with a first composition comprising an effective anti-acne amount of an organic peroxide in combination with an aqueous gel comprising about 40-75% water, about 0.25-5% of an inorganic gelling agent, and about 2.5-10% of a mixture of an inorganic emollient oil and an emollient organic ester.
7. The method according to claim 6, wherein the first composition further comprises about 0.025-0.25% of an amphoteric surfactant.
8. The method according to claim 7, wherein the first composition further comprises about 10-20% of a (C₂-C₄)alkanol.

9. The method according to claim 4, wherein the first applicator pad is impregnated with a first gelled composition comprising an effective anti-acne amount of an organic peroxide dispersed in about 50-80% water in combination with an effective amount of an inorganic gelling agent.
10. The method according to claim 4, wherein the first applicator pad is impregnated with a first gelled anhydrous composition comprising an effective anti-acne amount of an organic peroxide, about 75-90% of a mixture of inorganic and organic emollient oils, and about 1-10% of an inorganic gelling agent.
11. The method according to claim 10, wherein the composition further comprises about 0.1-1% of an amphoteric surfactant.
12. The method according to claim 4, wherein the second dermatological agent is an effective anti-acne amount of an antibiotic selected from the group consisting of erythromycin, tetracycline, clindamycin and the pharmaceutically acceptable salts thereof.
13. The method according to claim 12, wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt thereof.
14. The method according to claim 12, wherein the second composition comprises about 0.1-5% of the antibiotic dissolved or dispersed in mixture of water and a water-miscible organic solvent.

15. The method according to claim 14, wherein the second composition comprises an emulsion of about 0.1-5% clindamycin, erythromycin or a pharmaceutically acceptable salt thereof, about 80-95% aqueous alcohol and about 5-15% emollient organic esters.
16. The method according to claim 2, wherein the first dermatological agent is an effective keratolytic amount of salicylic acid.
17. The method according to claim 16, wherein the second dermatological agent is an effective anti-acne amount of an antibiotic.
18. The method according to claim 16, wherein the first composition comprises an aqueous-alcohol gel comprising about 0.5-10% salicylic acid.
19. The method according to claim 17, wherein the gel comprises about 0.5-5% of an organic gelling agent.
20. The method according to claim 2, wherein the first dermatological agent is an effective anti-acne amount of retinoic acid.
21. The method according to claim 20, wherein the first dermatological composition comprises about 0.01-0.25% retinoic acid.
22. The method according to claim 21, wherein the first dermatological composition further comprises a gelled mixture of water with a water-miscible organic solvent.

23. The method according to claim 20, wherein the first dermatological composition comprises about 0.01-0.25% retinoic acid, about 50-85% water, about 4-12% emollient oil, about 3-10% emollient wax stabilizer, about 5-20% polyhydric alcohol emollient and about 0.5-10% organic, water-soluble surfactant.
24. The method according to claim 20, wherein the second dermatological composition comprises an effective amount of one or more sunscreen compounds.
25. The method according to claim 20 wherein the second dermatological composition comprises about 50-85% water, about 4-12% emollient oil, about 3-10% emollient wax stabilizer, about 5-20% polyhydric alcohol emollient and about 0.5-10% organic, water-soluble surfactant.
26. The method according to claim 2, wherein the first dermatological composition comprises an effective amount of one or more sunscreen compounds.
27. The method according to claim 26, wherein the second dermatological composition comprises an effective amount of one or more sunscreen compounds.
28. The method according to claim 2, wherein the first composition is a pigment-containing wax-based cosmetic composition and the second composition is a make-up remover composition comprising a wax-free mixture of about 25-75% water, about 15-70% of a water-insoluble liquid emollient oil and an amount of a surfactant effective to stabilize the mixture as a homogeneous emulsion.

29. The method according to claim 28, wherein the first applicator pad is a hydrophilic polyurethane foam pad.
30. The method according to claim 2, wherein the first dermatological agent is an effective dermatological amount of corticosteroid.
31. The method according to claim 30, wherein the corticosteroid is dispersed throughout the first applicator pad as a powder.
32. The method according to claim 30, wherein the first applicator pad is impregnated with a corticosteroid in combination with a pharmaceutically acceptable carrier.
33. The method according to claim 2, wherein the second dermatological agent is an antihistamine, an antibiotic, an antifungal agent, a sunscreen, an emollient or a film-forming polymer.
34. A method for applying at least two phases of a film-forming composition comprising a therapeutic agent to the skin from one dispensing and applicator system, comprising the steps of:
 - (a) providing a dispensing and applicator system, comprising:
 - (1) a flexible, moisture impermeable support sheet;
 - (2) a plurality of applicator pads affixed in a separated array to the surface of said support sheet; each of said pads being impregnated with a different phase of the film-forming composition, a first phase comprising a solution of a barrier polymer,

and a second phase comprising one or more emollient oils; and

- (3) a flexible, moisture-impermeable cover sheet having its peripheral surface releasably sealed to the opposed peripheral surface of the support sheet so as to form a compartment containing said pads and defined by a continuous seal, which seal is positioned inwardly from the edges of the sheets over a portion of the opposed peripheral surfaces, so as to form two opposed flanges, and wherein the cover sheet and the support sheet are also releasably sealed together between said pads to divide the compartment into a plurality of subcompartments, each containing one of said pads;
- (b) manually grasping and separating the flanges to at least partially release the cover sheet from the support sheet, so that said pads are exposed; and
- (c) contacting two or more of said pads with the skin to release the compositions sequentially or essentially simultaneously from the pads, at least one pad being impregnated with the first phase comprising the polymer solution, and at least one pad being impregnated with the second phase comprising the emollient solution, at least one of said solutions containing an effective amount of the therapeutical agent, to thereby apply a mixture of said solutions to form an occlusive or semi-occlusive film over the skin, the film retaining the therapeutical agent in intimate contact with the skin.

35. The method according to claim 34, wherein the first and second phases are released essentially simultaneously from the pads.
36. The method according to claim 34, wherein a first applicator pad impregnated with the first phase comprising the barrier polymer, and a second applicator pad impregnated with the second phase comprising the emollient solution, are affixed to one surface of said support sheet.
37. The method according to claim 36, wherein the first phase comprises about 15-50% barrier polymer and about 50-85% of a compatible solvent.
38. The method according to claim 1, wherein the barrier polymer is polyvinylpyrrolidone, an alkylated vinylpyrrolidone, a copolymer of vinylpyrrolidone, a polyquaternary polyvinylpyrrolidone, a methyl vinyl ether/maleic anhydride copolymer, a polyvinylidene chloride, or a combination thereof.
39. The method according to claim 38, wherein the copolymer of vinylpyrrolidone is vinylpyrrolidone/eicosene copolymer, vinylpyrrolidone/hexadecene copolymer, vinylpyrrolidone/vinyl acetate copolymer, vinylpyrrolidone/dialkylaminoacrylate copolymer, vinylpyrrolidone/dimethylaminoethyl-methacrylate copolymer, or a combination thereof.

40. The method according to claim 1, wherein the barrier polymer is a polysaccharide polymer selected from the group consisting of cellulose, starches, chitins, chitosans, alginates, carrageenans, agars, agaroses, locust bean gums, konjacs, and derivatives thereof, and combinations thereof.
41. The method according to claim 36, wherein the first phase further comprises an effective amount of the therapeutical agent.
42. The method according to claim 41, wherein the first phase comprises about 0.5-5% of the therapeutical agent.
43. The method according to claim 34, wherein the therapeutical agent is selected from the group consisting of an anti-inflammatory agent, a topical antipruritic, an anti-psoriatic agent, a keratolytic agent, a local anaesthetic agent, an anti-acne agent, and a wart-removing agent.
44. The method according to claim 43, wherein the therapeutical agent is selected from the group consisting of aspirin, camphor, bufexamac, a steroid, anthralin, coal tar extract, salicylic acid, urea, lidocaine, benzocaine, benzoyl peroxide, a vitamin A derivative, lactic acid, or a combination thereof.
45. The method according to claim 44, wherein the therapeutical agent is a steroid selected from the group consisting of hydrocortisone, hydrocortisone acetate, hydrocortisone valerate, hydrocortisone butyrate, desonide, triamcinolone acetonide, betamethasone valerate, betamethasone dipropionate,

betamethasone benzoate, clobetasol propionate, halcinonide, desoximethasone, amcinonide, fluocinonide, fluandrenolide, alclometasone dipropionate, fluocinolone acetonide, diflorasone diacetate, mometasone furoate, fluorometholone, clocortolone pivalate, triamcinolone acetonide, and halcinonide.

46. The method according to claim 34, wherein the second phase comprises about 5-50% of one or more emollient oils and about 50-90% aqueous alcohol.
47. The method according to claim 34, wherein at least one phase comprises an effective amount of a penetration enhancing agent.
48. The method according to claim 47, wherein the penetration enhancing agent is dimethyl sulfoxide, N,N-dimethyl acetamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, carbitol solvent, propylene carbonate, 1,5-dimethyl-2-pyrrolidone, or 2-pyrrolidone-5-carboxylic acid.
49. The method according to claim 34, wherein at least one phase comprises about 0.25-5% of an inorganic gelling agent.
50. The method according to claim 34, wherein the film is maintained on the skin for a time effective to deliver the therapeutical agent transdermally through the skin.
51. The method according to claim 34, wherein the skin surface is moist with an aqueous medium.

52. The method according to claims 1 or 34, wherein the cover sheet is scored along lines between said pads so that in step (b), the flanges abutting one subcompartment are separated so that the cover sheet tears along said score lines of the cover sheet and separates from the support sheet to open one subcompartment and expose one of said pads, while the other subcompartments remain intact; and so that in step (c), the exposed pad is contacted with skin to release the composition from the exposed pad onto the skin.
53. The method according to claims 1 or 34, wherein the support sheet is scored along lines between said pads so that in step (b), the flanges abutting one subcompartment are separated so that the support sheet tears along said score lines of the support sheet and separates from the cover sheet to open one subcompartment and expose one of said pads, while the other subcompartments remain intact; and so that in step (c), the exposed pad is contacted with skin to release the composition from the exposed pad onto the skin.
54. The method according to claims 1 or 34, wherein the cover sheet and support sheet are made of a deformable plastic coated foil.
55. The method according to claims 1 or 34, wherein the cover sheet and the support sheet are sealed together by heat sealing or by an adhesive.
56. The method according to claims 1 or 34, wherein the applicator pads are made of synthetic fiber, natural fiber, or foam.

57. A dispensing and applicator system for applying a plurality of dermatological agents, comprising:
- (a) a flexible, moisture impermeable support sheet;
 - (b) a plurality of applicator pads affixed in a separated array to the surface of said support sheet; each of said pads being impregnated with a composition comprising a different dermatological agent; and
 - (c) a flexible, moisture-impermeable cover sheet having its peripheral surface releasably sealed to the opposed peripheral surface of the support sheet so as to form a compartment containing said pads and defined by a continuous seal, which seal is positioned inwardly from the edges of the sheets over a portion of the opposed peripheral surfaces, so as to form two opposed flanges, and wherein the cover sheet and the support sheet are also releasably sealed together between said pads to divide the compartment into a plurality of subcompartments, each containing one of said pads; the flanges being separable to at least partially release the cover sheet from the support sheet, so that said pads are exposed.
58. A dispensing and applicator system for applying at least two phases of a film-forming composition comprising a therapeutical agent, comprising:
- (a) a flexible, moisture impermeable support sheet;
 - (b) a plurality of applicator pads affixed in a separated array to the surface of said support sheet; each of said pads being impregnated with a different phase of the film-forming composition, a first phase comprising a solution of a barrier polymer, and a second phase comprising one or more emollient oils; at least one pad being impregnated

with the first phase comprising the polymer solution, and at least one pad being impregnated with the second phase comprising the emollient solution, at least one of said solutions containing an effective amount of the therapeutical agent;

wherein said solutions upon application to a skin surface form an occlusive or semi-occlusive film over the skin to retain the therapeutical agent in intimate contact with the skin; and

- (c) a flexible, moisture-impermeable cover sheet having its peripheral surface releasably sealed to the opposed peripheral surface of the support sheet so as to form a compartment containing said pads and defined by a continuous seal, which seal is positioned inwardly from the edges of the sheets over a portion of the opposed peripheral surfaces, so as to form two opposed flanges, and wherein the cover sheet and the support sheet are also releasably sealed together between said pads to divide the compartment into a plurality of subcompartments, each containing one of said pads; the flanges being separable to at least partially release the cover sheet from the support sheet, so that said pads are exposed.

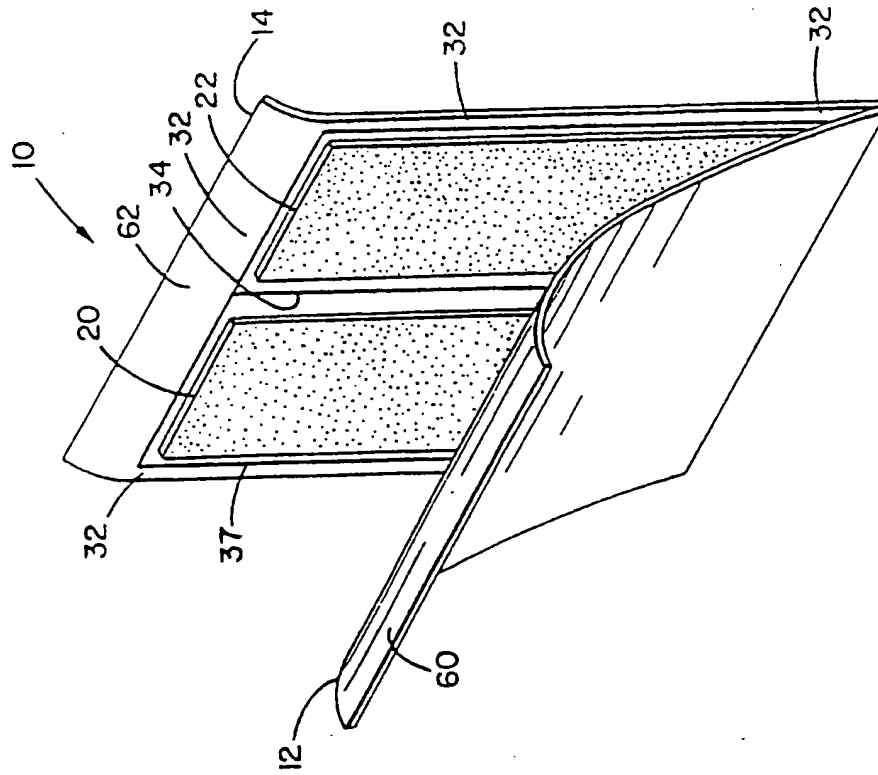


FIG. 2

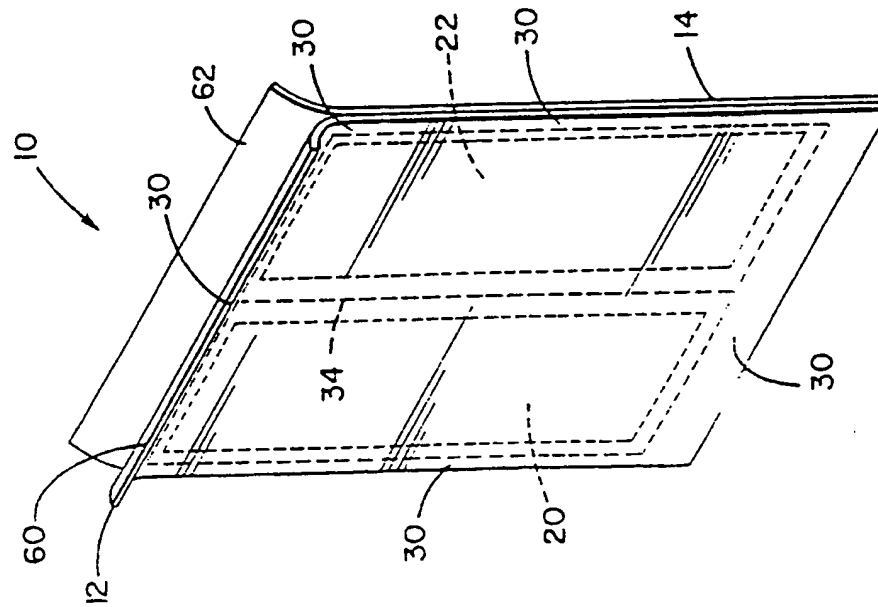


FIG. 1

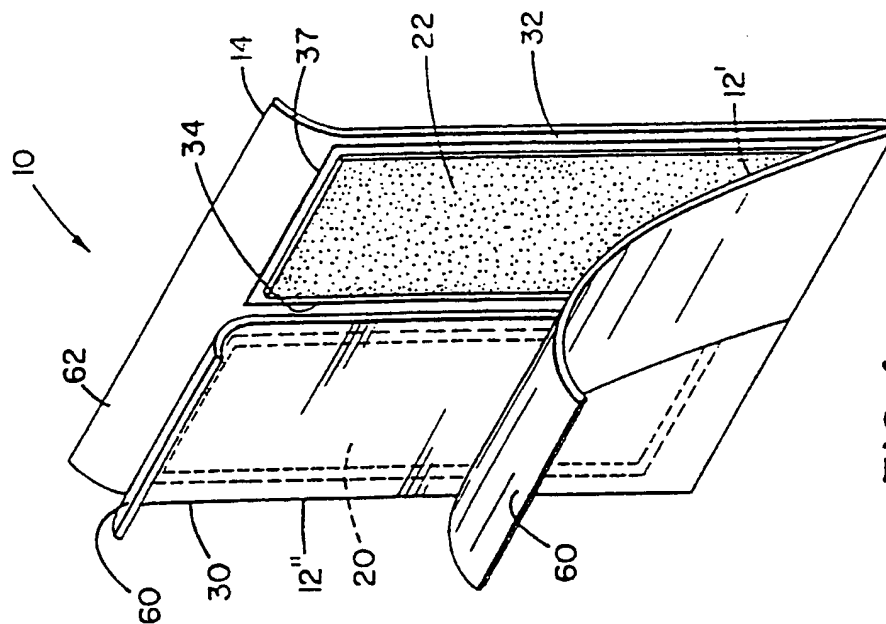


FIG. 4

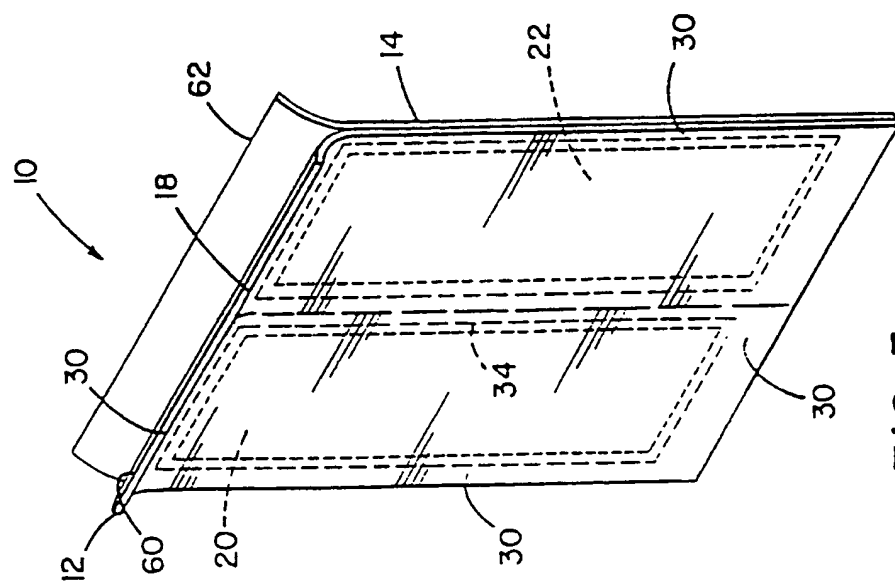


FIG. 3

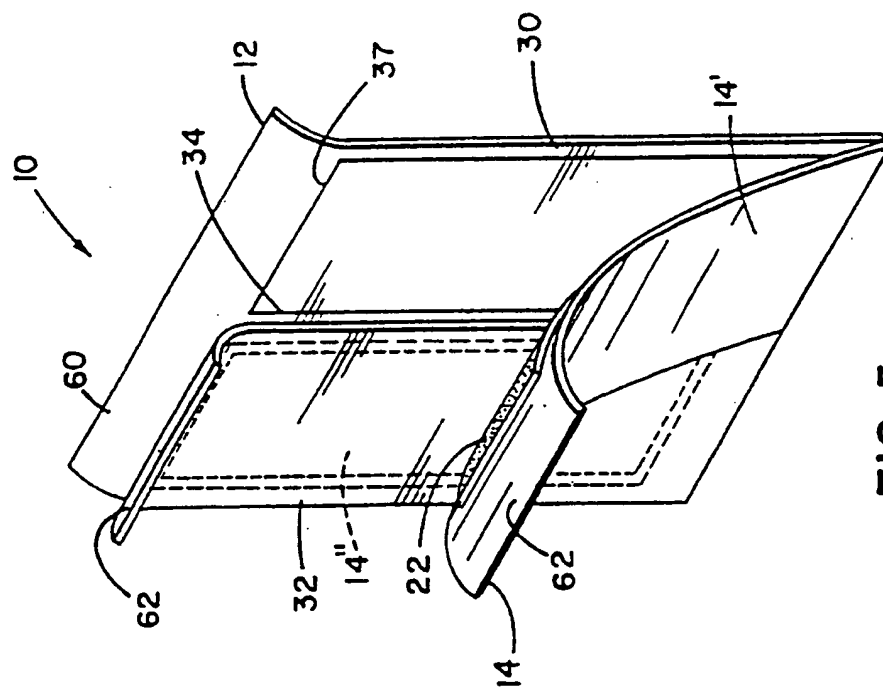


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11897

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 35/00

US CL :604/289

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/290, 304; 128/743; 602/57; 401/132; 514/859

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

None

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,889,804, (Ravich), 17 June 1975. See entire document.	57
Y	US, A, 4,372,098, (Mason), 08 February 1983. See entire document	57
A	US, A, 4,796,751, (Madkour), 10 January 1989. See entire document.	

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

15 FEBRUARY 1994

Date of mailing of the international search report

21 APR 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

PAUL PREBILIC

Telephone No. (703) 308-2905

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.